Title & Detailed Synopsis of the Proposed Ph.D. Thesis

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DEVELOPMENT OF GREEN SYNTHETIC PROTOCOLS FOR BIOLOGICALLY RELEVANT HETEROCYCLES

a) Origin of the research problem

Heterocycles belong to a spectacular class of organic compounds well-known for their inherent biological activity and applications in diverse fields, reflected by the fact that this class of compounds constitutes more than half of known organic molecules. Although heterocyclic compounds find wide range of applications but are of particular interest in medicinal chemistry, which has catalyzed the discovery and development of much heterocyclic chemistry and methods. Heterocyclic moieties are widely prevalent in pharmaceuticals, agrochemicals, dyes and many other application-oriented materials. Recently, it has been estimated that approximately more than 70% of all the enlisted pharmaceuticals and agrochemicals bear at least one heterocyclic ring. It may be mentioned in this connection that some of the biggest commercial products to date, such as the blockbuster blood cholesterol reducer atorvastatin (Lipitor®) for the treatment of dyslipidemia and the prevention of cardiovascular diseases and the broad-spectrum fungicide azoxystrobin (Amistar®), currently in use against diseases of more than 100 different crops in more than 100 different countries, belong to this huge heterocyclic group of active ingredients. Heterocycles can also serve as prodrug functionalities as exemplified in the thienopyridine class of antiplatelet agents, clopidogreal and prasugrel. The versatility of heterocycles in modern drug discovery is amply demonstrated in these new drugs. Furthermore, heterocycles seem to be perfect bioisosteres of other iso- or heterocyclic rings as well as of several different functional groups, in most cases, delivering through their similarity in structural shape and electronic distribution equal or even better biological efficacy. Synthesis of a wide variety of heterocycles and their functionalized derivatives coupled with assessment of their biological evaluation is, thus a very promising field to the organic and medicinal chemists at large. That is why a huge library of synthetic heterocycles is available!

The twentieth century was highly successful in this regard. However, with the advent of the twenty-first century, the public is equally aware of the hazardous substances used and generated by the chemical processes. Our natural environment needs to be protected from ever increasing chemical pollutions associated with contemporary lifestyles and emerging technologies. The fundamental challenge for developing a sustainable chemical enterprise will be finding creative ways to minimize human exposure to, and the environmental impact of, harmful chemicals while enhancing scientific progress. A new approach emphasizing pollution prevention through the design and use of cleaner products and processes can help the chemical enterprise to achieve a sustainable future. Hence, a concept of "*Green Chemistry*" or "*Environmentally Benign Chemistry*" has been developed, which focuses on the designing of chemical products and processes that can reduce or eliminate the use and generation of hazardous substances, eventually preventing the pollution at large. Anastas and Warner developed "*The Twelve Principles of Green Chemistry*" which can serve as guidelines for practicing chemists in developing and assessing how green a synthesis, compound, process, or technology is. The last decade has seen

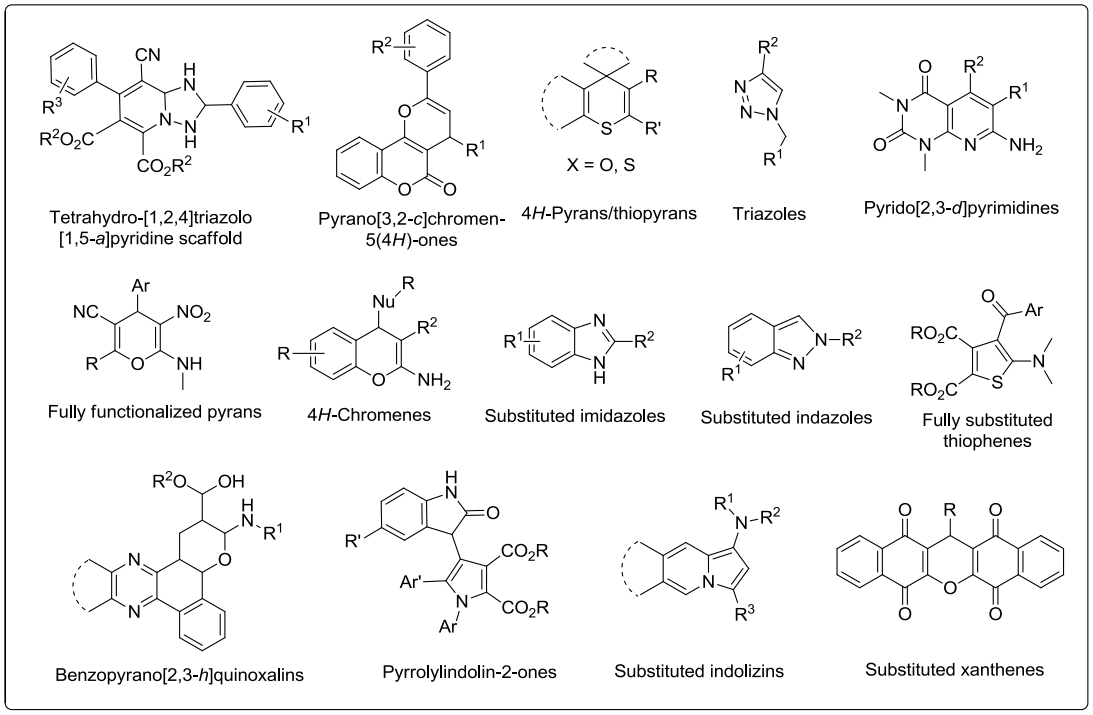
a huge interest in green chemistry, particularly as organic chemists look to "*green*" the methodologies/techniques for the synthesis of organic molecules of interest! As a result, several methodologies/concepts such as solvent-free synthesis, organic reactions under aqueous conditions, greener organic reagents, development of heterogeneous catalysts and ionic liquids, waste management/recycling strategies, application of ultrasound, and microwave technology as a greener heating tool have emerged and are in extensive use at present-time.

Very particularly, the sixth principle is devoted to "*Design of Energy Efficiency*"! That is to develop synthetic strategies that require less/minimum amount of energy to carry out a specific reaction with optimum productivity. During large-scale industrial production, energy usage is also a vital concern! For this purpose, use of microwave and application of ultrasound are in use as substitutes of conventional heating. Recently, organic synthesis using ball-milling has attained popularity because this technique avoids the use of solvent and extraneous heating. In spite of admitting the utility of using these energy-efficient aids (such as ultrasound irradiation, grinding/ball-milling), we should also turn our attention to design protocols at ambient temperature because the most effective way-out to save energy is to develop strategies/protocols that are capable enough to carry out the transformations at room temperature! In addition, room temperature condition is the mildest reaction condition, essentially required for many temperature-sensitive organic substrates as a key step in multi-step sequence reactions. That's why, as part of on-going developments on green synthetic strategies, designing for room temperature conditions coupled with other green aspects is also an area of current choice. Under this purview, the present investigator has been motivated to undertake research in this remarkable field of interest with a motto to design and develop novel protocols for the syntheses of biologically relevant heterocycles under energy-efficient manner coupled with other significant green chemistry parameters.

b) Objectives of the present work plan

- To develop eco-friendly MCR methodologies to achieve high atom-economy, avoiding multi-step complex processes either at room temperature and atmospheric pressure or under the direct application of any of the alternative energy sources
- To perform heterocycles synthesis under focused ultrasound irradiation
- To perform heterocycles synthesis using ball-milling technique
- To use nontoxic/less toxic and easily available chemicals as starting materials
- To use environmentally benign, cost-effective and easily available catalysts that could be recycled and reused
- To develop non-toxic or less toxic catalyst-systems
- To use water and/or aqua-organo mixture (e.g. water-ethanol) as solvent
- Easy purification of the final products avoiding chromatographic separation

Some targeted heterocyclic scaffolds of interests:



Scheme 1: Some targeted heterocyclic scaffolds of our interest

Point-wise summary of the major parts of the present work plan:

- Selection of targeted heterocyclic motif (**Scheme 1**) and designing its functionalized libraries
- Retroanalysis of the target motif and selection of cheap and commercially available substrates
- Designing for energy-efficient reaction protocols: optimization of catalyst and solvent media under suitable energy-efficient technique preferentially
    - at room temperature
    - under ball-milling
    - under ultrasound irradiation
- Application of the newly developed protocol in synthesizing more complex libraries of interest

Planning to consider few more green chemistry parameters like:

- introduction of novel one-pot multicomponent technique
- to verify the reaction under catalyst-free condition
- use of efficient, non-toxic, commercially available, cheap catalyst
- use of solvent-free condition or to use suitable green solvents like water/ethanol/glycerol/PEG

c) General methodology to be followed

Simple experimental set-up is to be developed for one-pot syntheses of targeted heterocycles (**Scheme 1**). The substrates and the catalyst (or catalyst free condition) will be added in a reaction vial (at a time or in a sequential manner). If needed suitable solvent will be added into the reaction mixture. The reaction mixture will be stirred magnetically at room temperature. The progress of the reaction will be monitored by TLC/PMR. After completion, the reaction mixture will be settled down and the solvent will be removed under reduced pressure, and the residue will be purified simply by recrystallization and/or by column chromatographic technique. For characterization of the synthesized heterocycles, their detailed spectral studies including FT-IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, HR-MS as well as elemental analyses will be performed. In certain cases, X-ray analysis of unit crystals as to be developed of the products will also be taken care of! Similar method will be used in case of ultrasonic irradiation.

Under grinding condition the reagents, substrates and catalyst (normally solid basic support) will be mixed in a ball-miller under solvent free condition. By definite programming, the reaction mixture will be subjected to grinding with pre-given speed and time. Before introduction of the reaction mixture, the particular ball-size will be chosen. After the completion, the reaction routine work up procedure will be followed to get the final products.

d) Future prospect

The research outcomes would embody a considerable amount of new works relating to the development of green methodologies for a number of novel biologically relevant heterocyclic compounds which would attract researchers from various multi-disciplinary fields for their further studies, particularly on the physio-chemical properties, *in silico* biological potentials, experimental (*in vitro* and *in vivo*) studies on their potential pharmaceutical efficacies and also use of the protocols as developed for library synthesis of lead drug candidates.

e) References

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